

Office of Clinical Pharmacology NDA Review	
Number	205-383, SDN 18
Type/Category	Resubmission/Class 2 / Original-1 (Type 3- New Dosage Form)
Brand (generic) Name	OralTag (Iohexol Powder for Oral solution)
Proposed Indication	Oraltag: <ul style="list-style-type: none"> is indicated for oral use in adults and children as an opacification agent during computed tomography of the abdomen and pelvis. <div style="background-color: #cccccc; width: 100%; height: 1.2em; text-align: right;">(b) (4)</div>
Dosage Form	Powder for Solution
Route of Administration	Intravenous
Dosing Regimen and Strength	Adults: 1 or 2 bottles of prepared solution (4.5 gI or 9 gI). Prepared at a concentration of 9 mgI/mL, the volume is 500 mL (1 bottle) or 1000 mL (2 bottles). Children: 1 or 2 bottles of prepared solution (4.5 gI or 9 gI). Prepared at a concentration of 9 mgI/mL, the recommended volume is (b) (4) mL to 750 mL; for neonates, infants and toddlers a lesser volume, e.g., less than (b) (4) mL up to 300 mL, may be sufficient. The total oral dose in grams of iodine should generally not exceed 1 bottle (children under 3 years of age) or 2 bottles (children 3 to 18 years of age).
Applicant	(b) (4)
OCP Division	DCP V
OND Division	DMIP
Submission Dates	September 26, 2014

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1. EXECUTIVE SUMMARY

The Applicant is seeking approval of NDA 205-383 for OralTag (Iohexol Powder for Oral Solution) under the 505(b)(2) regulatory pathway according to 21 CFR 314.54 as agreed to at the pre-NDA meeting held on March 20, 2012. The approved reference listed product is Omnipaque Oral Solution.

No new clinical or clinical pharmacology studies were conducted in support of this NDA submission.

An earlier submission with the same content as the current submission received a Complete Response (CR) letter on January 8, 2014 due to product quality issues. Dr. Safaa Burns reviewed the prior submission (DARRTS date of Dr. Burns' review is October 29, 2013). Dr. Burns performed a review of the package insert, however, edits to the package insert were not finalized by the Medical Division because of the decision to issue a CR letter. This reviewer has made some additions and minor edits over Dr. Burns' edits. Our recommendations for the package insert are shown in Section 3 of this review.

1.1. RECOMMENDATIONS

The application is acceptable from a clinical pharmacology perspective provided that agreement on package insert language can be reached.

1.2 POST-MARKETING COMMITMENTS AND REQUIREMENTS

None.

Signatures:

Christy S. John, Ph.D.
Reviewer
Division of Clinical Pharmacology V

Gene Williams, Ph.D.
Team Leader
Division of Clinical Pharmacology V

1.3. SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

There are no clinical pharmacology findings -- no new clinical or clinical pharmacology studies were conducted in support of this NDA submission.

2. QUESTION-BASED REVIEW

Question-based review is not applicable -- no new clinical or clinical pharmacology studies were conducted in support of this NDA submission.

3. DETAILED LABELING RECOMMENDATIONS

The entirety of the applicant's proposed package insert is appended to this review as Appendix 4.1. The changes to the clinical pharmacology related sections of the package insert are given below (**FDA Table 1.**)

FDA Table 1. Detailed Labeling Recommendations		
Approved Labeling for Omnipaque Oral Solution (Most Recent Version: May 2010)	Applicant's Proposed PLR Labeling for Iohexol Powder for Oral Solution	Reviewer's Revisions to Applicant's Proposed PLR Labeling
<p>Drug/Laboratory Test Interaction</p> <p>If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine binding capacity of thyroid tissue may be reduced for up to 2 weeks after contrast medium administration.</p> <p>Thyroid function tests which do not depend on iodine estimation, eg, T3 resin uptake or direct thyroxine assays, are not affected.</p> <p>Many radiopaque contrast agents are incompatible <i>in vitro</i> with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.</p>	(b) (4)	(b) (4)
		[entirety of section moved to Section 5.2]

	<p>8 USE IN SPECIFIC POPULATIONS</p> <p>(b) (4)</p>	<p>8 USE IN SPECIFIC POPULATIONS</p> <p>[entirety of section deleted, not needed] (b) (4)</p> <p>[entirety of section deleted, not needed] (b) (4)</p>
<p>CLINICAL PHARMACOLOGY</p> <p>For most body cavities, the injected iohexol is absorbed into the surrounding tissue and eliminated by the kidneys and bowel as previously described in SECTION II, CLINICAL PHARMACOLOGY—</p> <p>Intravascular.</p> <p>Examinations of the uterus (hysterosalpingography) and bladder (voiding cystourethrography) involve the almost immediate drainage of contrast medium from the cavity upon conclusion of the radiographic procedure.</p> <p>Orally administered iohexol is very poorly absorbed from the</p>	<p>12 CLINICAL PHARMACOLOGY</p>	<p>12 CLINICAL PHARMACOLOGY</p>

<p>normal gastrointestinal tract. Only 0.1 to 0.5 percent of the oral dose was excreted by the kidneys. This amount may increase in the presence of bowel perforation or bowel obstruction. Iohexol is well tolerated and readily absorbed if leakage into the peritoneal cavity occurs.</p> <p>Visualization of the joint spaces, uterus, fallopian tubes, peritoneal herniations, pancreatic and bile ducts, and bladder can be accomplished by direct injection of contrast medium into the region to be studied. The use of appropriate iodine concentrations assures diagnostic density.</p> <p>Orally administered OMNIPAQUE produces good visualization of the gastrointestinal tract. OMNIPAQUE is particularly useful when barium sulfate is contraindicated as in patients with suspected bowel perforation or those where aspiration of contrast medium is a possibility.</p>	<p>Orally administered iohexol is very poorly absorbed from the normal gastrointestinal tract. Only 0.1 to 0.5% of the oral dose (b) (4) excreted by the kidneys. This amount may increase in the presence of bowel perforation (b) (4) bowel obstruction or severe inflammatory bowel disease. (b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p>	<p>12.1 Mechanism of Action Iohexol enhances imaging through attenuation of photons. Different tissues within the body attenuate the beam of X-rays to different degrees. The enhanced visualization is due to the iodine present in the tissue of interest.</p> <p>12.3 Pharmacokinetics Orally administered iohexol is very poorly absorbed from the normal gastrointestinal tract. Only 0.1 to 0.5% of the oral dose is excreted by the kidneys. This amount may increase in the presence of bowel perforation, bowel obstruction, or severe inflammatory bowel disease.</p>
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	<p style="text-align: center;">(b) (4)</p> <p>IoHexol displays a low affinity for serum or plasma proteins and is poorly bound to serum albumin. No significant metabolism, deiodination or biotransformation occurs.</p>	<p>IoHexol displays a low affinity for serum or plasma proteins and is poorly bound to serum albumin. No significant metabolism, deiodination or biotransformation occurs.</p>
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4. APPENDICES

4.1 Applicant's Proposed Package Insert

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY S JOHN
02/25/2015

GENE M WILLIAMS
02/25/2015

I concur with the recommendations.